REMARKS

Claims 18-23 have been canceled in this Amendment. New Claims 25-30 have been added. The subject matter in Claims 25-30 is supported by the specification and the claims as originally field. No new matter is added in through this Amendment.

35 U.S.C. §102(b)

The Examiner rejected Claims 18 and 20-21 under 35 U.S.C. §102(b) as being anticipated by Bombardelli et al. To anticipate a claim, the reference must teach every element of the claim. M.P.E.P §2131. Claims 18 and 20-21 have been canceled. New Claims 25-30 are directed toward colchicine or thiocolchicoside, in combination with an anti-proliferative agent. Bombardelli teaches compositions comprising colchicine derivatives which possess antiproliferative activities. Bombardelli does not teach a composition comprising colchicine or a colchicine analog in combination with **an additional** agent with antiproliferative properties. Therefore, Bombardelli does not anticipate new Claims 25-30.

The Examiner rejected claims 18-19 and 23 under 35 U.S.C. §102(b) as being anticipated by Joseph. Joseph teaches a drug preparation for treating wounds, wherein the preparation consists essentially of a drug carrier, paclitaxel, penicillamine and colchicine. Claims 18-19 and 23 have been canceled. The new claims do not claim colchicine in combination with paclitaxel or penicillamine. As such the new claims are not anticipated by Joseph.

The Examiner rejected claims 18-19 and 23 under 35 U.S.C. §102(b) as being anticipated by Horrobin. Horrobin teaches the use of thioproline and alpha-linolenic acid to control fatty acid metabolism to treat cancer. Variations on the composition in Horrobin include colchicine or colchicine in combination with additional agents including vinblastine. Claims 18-19 and 23 have been canceled. The new claims do not claim colchicine in combination with thioproline, alpha-linolenic acid or vinblastine As such the new claims are not anticipated by Horrobin.

The Examiner rejected claims 18-19 and 22 under 35 U.S.C. §102(b) as being anticipated by Ratain et al. Ratain teaches the use of colchicine to reduce the toxicity of camptothecin. Claims 18-19 and 22 have been canceled. The new claims do not claim colchicine in combination with camptothecin. As such the new claims are not anticipated by Ratain.

The Examiner rejected claims 18-19 under 35 U.S.C. §102(b) as being anticipated by Fong et al. Fong teaches the combination of colchicine and doxorubicin to kill multi-drug resistant cancer cells. Claims 18-19 have been canceled. The new claims do not claim colchicine in combination with doxorubicin. As such the new claims are not anticipated by Ratain.

The Examiner rejected claims 18 and 20 under 35 U.S.C. §102(b) as being anticipated by Belisario et al. Belisario teaches the combination of demecolcin and N-deacetyl thiocolchicine for treatment of cutanous cancer and precancer. Claims 18 and 20 have been canceled. The new claims do not claim the combination of demecolcin and N-deacetyl thiocolchicine. As such the new claims are not anticipated by Belisario.

35 U.S.C. §103(a)

The Examiner rejected claims 18 -21 under 35 U.S.C. §103(a) as being obvious over Bombardelli et al. There are three requirements to establish a *prima facie* case of obviousness: 1) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach or suggest all the claim limitations. M.P.E.P §2143. Bombardelli teaches compositions comprising colchicine derivatives which possess antiproliferative activities. Bombardelli does not teach a composition comprising colchicine or a colchicine analog in combination with **an additional** agent with antiproliferative properties. The Examiner asserts that it would have obvious to one of skill in the art to substitute colchicine for a colchicine derivative. What the Examiner does not explain is why one of skill in the art would be motivated to combine colchicine or a colchicine derivative with additional antiproliferative agents. The new claims recite a composition comprising colchicine or thiocolchicoside in combination with an additional antiproliferative agent. As such, the new claims are not obvious over Bombardelli.

The Examiner rejected claims 18-21 and 23 under 35 U.S.C. §103(a) as being obvious over Horrobin or Joseph. Joseph teaches a drug preparation for treating wounds, wherein the preparation consists essentially of a drug carrier, paclitaxel, penicillamine and colchicine. Horrobin teaches the

use of thioproline and alpha-linolenic acid to control fatty acid metabolism to treat cancer. Variations on the composition in Horrobin include colchicine or colchicine in combination with additional agents including vinblastine.

Claims 18-19 and 23 have been canceled. The new claims do not claim colchicine in combination with paclitaxel, penicillamine or vinblastine. Claim 25 is directed toward a composition comprising colchine and cisplatin. Claims 26-30 are directed toward thicolchicoside in combination with cisplatin, etoposide, camptothecin, vinblastine or paclitaxel. Joseph and Horrobin do not teach the compositions recited in the new claims. Applicant respectfully asserts that it would not be obvious to one of skill in the art to take the disclosure of Joseph or Horrobin and modify the teachings therein to arrive at the combinations recited in the new claims of the present application.

The Examiner rejected claims 18- 23 under 35 U.S.C. §103(a) as being obvious over Frisch, Houghton, and/or Raitain. New Claims 25-30 are directed toward colchicine or thiocolchicoside, in combination with an anti-proliferative agent. Frisch teaches use of the adenovirus E1A to sensitize humor tumor cells to chemotherapy or irradiation. Frisch provides a list of chemotherapeutic agents including colchicine, cisplatinum, etopside, camptothecin, and vinblastine. However, Frisch does not teach the combination of the chemotherapeutic agents. Houghton teaches the use of a potentiating agent, wherein the potentiating agent is a derivative of phenoxazine, to increase the uptake of cytotoxic agents, including colchicine, vinblastine, etoposide. Houghton does not teach the combination of the cytotoxic agents. Ratain teaches the use of colchicine to reduce the toxicity of camptothecin. The new claims do not claim colchicine in combination with camptothecin.

The Examiner cites these references together to teach the individual components claimed. However, even when taken in combination, the references do not teach the compositions as now claimed in new Claims 25-30. The Examiner cites *In re Sussman,* for the proposition that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients. However, a showing of "synergism" or other extra-statutory tests for patentability are not required when claiming a composition comprising known ingredients. See for example *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 220 USPQ 97 (Fed. Cir. 1983) (There is no special patentability standard for ``combination" patents or inventions.); *Smiths Industries Medical Systems Inc. v. Vital Signs Inc.,* 183 F.3d 1347, 1356, 51 USPQ2d 1415, 1420-21 (Fed. Cir. 1999) (``there is no basis for concluding

that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention. ... Instead, the relevant inquiry is whether there is a reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references, and that would also suggest a reasonable likelihood of success."); *Nordberg Inc. v. Telsmith, Inc.*, 881 F. Supp. 1252, 1293, 36 USPQ2d 1577, 1611 (E.D. Wis. 1995), aff'd, 82 F.3d 394, 38 USPQ2d 1593 (Fed. Cir. 1996) (``Historically, where the claimed nonobviousness of an invention rested upon a new combination of old elements existing in the prior art, the claimed invention had to pass a severe test of nonobviousness consonant with the difficulty and improbability of finding invention in the assembly of old elements. ... This led some courts to require that the invention be `synergistic', i.e., that the combination of old elements result in some unusual or surprising effect that was not expected. ... The Federal Circuit appears to have overruled this line of cases, however, finding there is no requirement of a synergistic effect and that there is no basis for treating combinations of old elements differently in determining patentability.").

In conclusion, the Applicant asserts that the cited prior art does not teach all of the elements of new Claims 25-30 and the Examiner has not provided any evidence showing motivation to combine the prior art to arrive at the compositions as recited in the new claims. As such Claims 25-30 are not obvious over the cited prior art.

Double-Patenting

The Examiner has provisionally rejected Claims 18-23 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 11-13 of copending Application No. 09/810,527. Applicant requests withdrawal of this rejection because Claims 18-23 of the present application have been canceled and Claims 11-13 of copending Application No. 09/810,527 have been canceled.

The Examiner has also provisionally rejected Claims 18-23 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 11-13 of copending Application No. 09/834,177. Applicant requests withdrawal of this rejection because Claims 18-23 of the present application and Claims 12-13 of copending Application No. 09/834,177 have been canceled. Allowed Claim 11 of copending Application No. 09/834,177 is directed to a composition comprising amonafide and cisplatin.

Applicant believes that new claims 25-30 are patentably distinct from the claims of the copending applications.

Information Disclosure Statement

Applicant notes that the Examiner did not consider reference no. C7, Marron Gasca, et al., submitted in the Information Disclosure Statement filed on March 10, 2003. The Examiner did not consider the C7 because the reference is a Spanish-language article for which no translation was provided. Applicant respectfully points out that MPEP§ 609(III)(A)(3) provides:

> Where the information listed is not in the English language, but was cited in a search report or other action by a foreign patent office in a counterpart foreign application, the requirement for a concise explanation of relevance can be satisfied by submitting an English-language version of the search report or action which indicates the degree of relevance found by the foreign office. This may be an explanation of which portion of the reference is particularly relevant, to which claims it applies, or merely an "X", "Y", or "A" indication on a search report.

Applicant directs the Examiner's attention to the PCT International Search Report for counterpart PCT application WO 02/056872 A3, in which the C7 reference was originally cited, for a statement as to its relevance.

Applicant respectfully requests that the present remarks be considered and submits that the claims are in condition for allowance. An early notification of such is requested . The Examiner is invited to call the undersigned attorney for discussion of any outstanding issues.

Respectfully submitted,

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Date September 26, 2003

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